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(54) Title: **ARYLOXY PIPERIDINYL INDOLES FOR TREATING DEPRESSION**

(57) Abstract: This invention provides aryloxy indole derivatives which are useful for the treatment of diseases affected by disorders of the serotonin-affected neurological systems, such as depression and anxiety, the compounds having formula (I) wherein R₁ is H or alkyl; R₂, R₃, and R₄ are H, alkyl, or halogen; X is H, halogen, CN, or C₁-C₆ alkoxy; Z is (CH₂)_n or carbonyl; n is 1 or 2; and the dashed line indicates an optional double bond; or a pharmaceutically acceptable salt thereof.

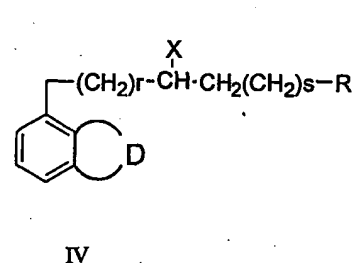
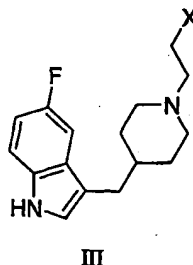
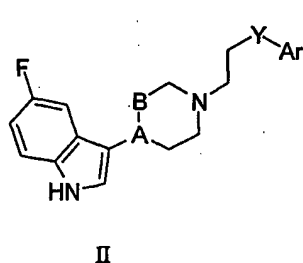
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ARYLOXY PIPERIDINYL INDOLES FOR TREATING DEPRESSION

This invention relates to new aryloxy indole derivatives as pharmaceuticals which are useful for the treatment in mammals of diseases affected by disorders of the serotonin-affected neurological systems, such as depression, anxiety, panic disorder, obsessive-compulsive disorder, sleep disorders, sexual dysfunction, bipolar disorders, psychosis, stress-related disorders, including post-traumatic stress disorders, Tourettes' syndrome, attention deficit disorder, with and without hyperactivity, alcohol and drug addiction, Alzheimer's disease, Parkinson's disease, obesity and acute and chronic pain, including migraine pain, as well as methods of enhancing cognition.

BACKGROUND OF THE INVENTION

EP 0714894 A1 discloses the preparation of compounds of formula II as new 5-HT_{1f} agonist for the treatment of migraine headaches. EP 429341 A2 claims compounds of formula III as having serotonin transporter activity. A recent publication by Malleron et al. was also reported based around formula I [J. Med. Chem. 36, 1194 (1993)]. EP 722941 A2 discloses compounds having effects on serotonin-related systems of formula IV.



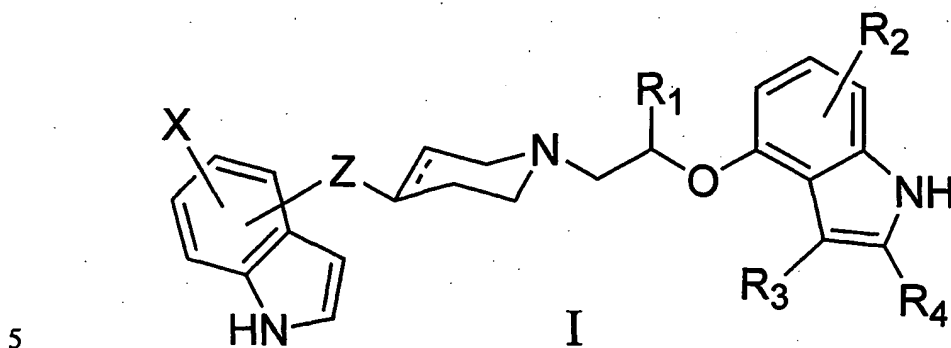
Pharmaceuticals which enhance serotonergic neurotransmission are of useful benefit for the treatment of many psychiatric disorders, including depression and

5 anxiety. The first generation of non-selective serotonin-affecting drugs operated through a variety of physiological functions which endowed them with several side effect liabilities. The more currently prescribed drugs, the selective serotonin (5-HT) reuptake inhibitors (SSRIs), act predominately by inhibiting 5-HT, which is released at the synapses, from being actively removed from the synaptic cleft via a presynaptic
10 serotonin transport carrier. Since SSRIs require several weeks before they exert their full therapeutic effect, this 5-HT blockade mechanism *per se* cannot account for their therapeutic activity. It is speculated that this two week induction which occurs before a full antidepressant effect is observed, is due to the involvement of the 5-HT_{1A} autoreceptors which suppress the firing activity of 5-HT neuron, causing a dampening
15 of the therapeutic effect. Studies suggest that after several weeks of SSRI administration, a desensitization of the 5-HT autoreceptors occurs allowing a full antidepressant effect in most patients. Recent studies by Artigas et al. (Trends Neurosci., 1996, 19, 378-383) suggest a combination of 5-HT_{1A} activity and inhibition of 5-HT uptake within a single molecular entity can achieve a more robust and fast-
20 acting antidepressant effect.

The present invention relates to a new class of molecules which have the ability to act at the 5-HT_{1A} autoreceptors and concomitantly with the 5-HT transporter. Such compounds are therefore potentially useful for the treatment of
25 depression as well as other serotonin disorders.

SUMMARY OF INVENTION

The compounds of this invention are aryloxy piperidinyl indoles represented
30 by Formula I:



wherein:

R_1 is hydrogen or alkyl of from 1 to 6 carbon atoms;

10 R_2 , R_3 , and R_4 are each independently selected from hydrogen, alkyl of from 1 to 6 carbon atoms or halogen;

X is selected from hydrogen, halogen, CN, or C_1 - C_6 alkoxy;

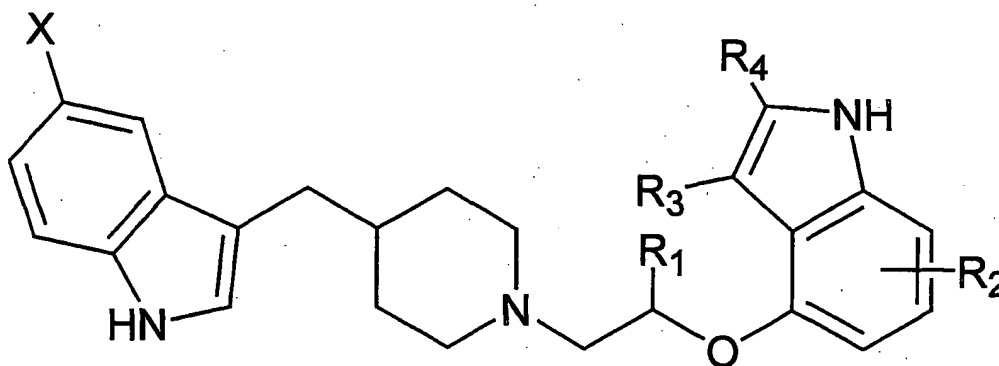
Z is $(CH_2)_n$ or carbonyl;

n is 1 or 2 ; and

the dashed line indicates an optional double bond;

15 or a pharmaceutically acceptable salt thereof.

One group of compounds of this invention comprises those of the formula:

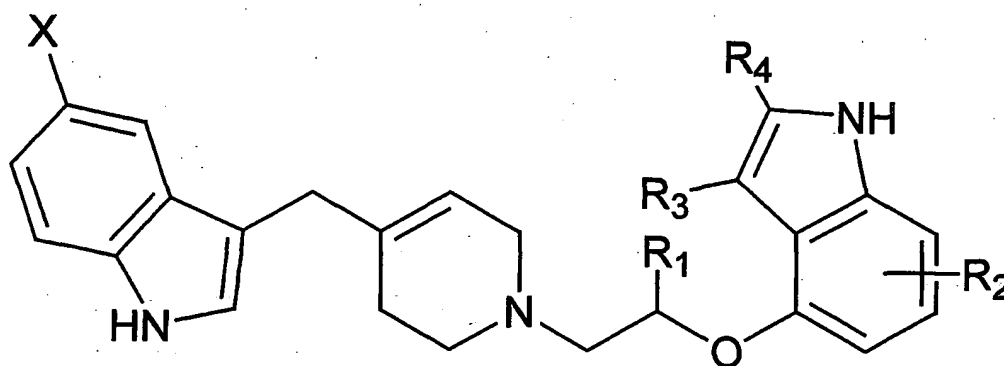


20 wherein:

X is selected from hydrogen, halogen, CN, or C_1 - C_6 alkoxy;

- 5 R_1 is hydrogen or alkyl of from 1 to 3 carbon atoms; and
 R_2 , R_3 , and R_4 are each independently selected from hydrogen, alkyl of from
 1 to 6 carbon atoms, or halogen;
 or a pharmaceutically acceptable salt thereof.

- 10 Another group of compounds of this invention comprise those of the formula:



wherein:

- X is selected from hydrogen, halogen, CN, or C_1-C_6 alkoxy;
 R_1 is hydrogen or alkyl of from 1 to 3 carbon atoms; and
 15 R_2 , R_3 , and R_4 are each independently selected from hydrogen, alkyl of from
 1 to 6 carbon atoms, or halogen;
 or a pharmaceutically acceptable salt thereof.

In the formulae disclosed herein:

- 20 Examples of R_1 are hydrogen and alkyl of 1 to 3 carbon atoms.
 R_2 , R_3 and R_4 may each independently represent hydrogen, alkyl of 1 to 3
 carbon atoms, chlorine or fluorine.
 Examples of X are hydrogen, fluorine, chlorine, CN and methoxy, e.g., in the
 5- or 6- position.
 25 Z may be for example $-CH_2-$ (i.e., n is 1). Z may be bonded to the indole ring
 in the 3-position.

5

The compounds of this Formula I also may be used in the form of a pharmaceutically acceptable acid addition salt having the utility of the free base. Such salts, prepared by methods well known to the art are formed with both inorganic or organic acids, for example: fumaric, maleic, benzoic, ascorbic, pantoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene-sulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

15

The compounds of formula I can possess an asymmetric centre and accordingly some compounds may exist and be isolated in optically active forms. This invention encompasses the compounds of formula I in any optically active or geometric form or mixtures thereof eg, racemates or enantiomers. Standard separation techniques may be used to isolate particular enantiomeric forms. For example a racemic mixture may be converted to a mixture of optically active diastereoisomers by reaction with a single enantiomer of a 'resolving agent' (for example by diastereomeric salt formation or formation of a covalent bond). The resulting mixture of optically active diastereoisomers may be separated by standard techniques (e.g crystallisation or chromatography) and individual optically active diastereoisomers then treated to remove the 'resolving agent' thereby releasing the single enantiomer of the compound of the invention. Chiral chromatography (using a chiral support, eluent or ion pairing agent) may also be used to separate enantiomeric mixtures directly.

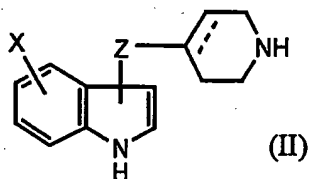
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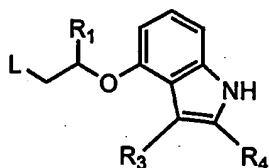
This invention also provides processes for preparing the compounds of formula (I) which processes comprise:

- a) reacting a compound of formula



5

wherein the dotted line X and Z are as defined above, with a compound of formula:



10

wherein R_1 , R_2 , R_3 and R_4 are as defined herein and is a leaving group such as halogen, e.g chlorine,

or

15

b) converting a basic compound of formula I to a an acid addition salt or vice versa.

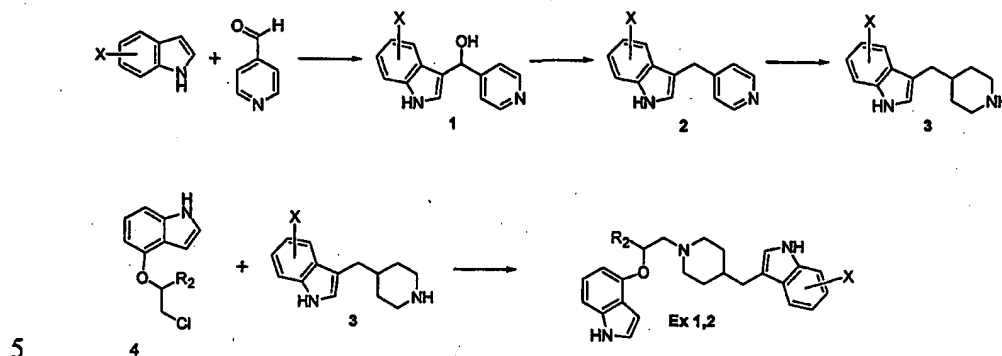
or

c) isolating an isomer of a compound of formula I from a mixture of isomers.

20

In detail the compounds of Formula I can be generally prepared by the overall sequence indicated in Scheme 1 as follows:

Scheme 1



The following examples for preparation of intermediates and invention compounds are included for illustrative purposes and are not to be construed as limiting to this disclosure in any way. Those skilled in the art of organic synthesis may be aware of still other synthetic routes to the invention compounds. The reagents and intermediates used herein are either commercially available or prepared according to standard literature procedures.

Intermediate 1

(5-Fluoro-1*H*-indol-3-yl)-pyridin-4-yl-methanol. To a stirred solution of 5-fluoroindole (3.10 g, 23.0 mmol) in methanol (10.0 mL) was added 4-pyridinecarboxaldehyde (2.20 mL, 23.0 mmol), followed by addition of NaOH (2.5 mL, 50%) at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for 3 h, followed by the addition of water (10.0 mL). The precipitate was collected by filtration and dried under vacuum to afford 5.2 g (93%) of a light yellow solid: mp 171-173 °C; ¹H NMR (DMSO, 400 MHz), δ 5.85 (d, 1H), 5.93 (d, 1H), 6.86-7.34 (m, 4H), 7.43 (dd, 2H), 8.48 (dd, 2H), 11.09 (br s, 1H); MS (EI) m/z 242 (M⁺); HRMS calcd for C₁₄H₁₂FN₂O [M+H] 243.09337, found 243.09576.

5

Intermediate 2

5-Fluoro-3-[(4-pyridinyl)methyl]-1*H*-indole. To a suspension of (5-fluoro-1*H*-indol-3-yl)-pyridin-4-yl-methanol (0.799 g, 3.3 mmol) in methylene chloride (13 mL) was added triethylsilane (0.60 mL, 3.7 mmol) followed by trifluoroacetic acid (2.85 mL, 37 mmol) at room temperature. After addition of trifluoroacetic acid, a clear black solution was obtained. The reaction mixture was stirred overnight and the solvent and excess trifluoroacetic acid was removed on a rotary evaporator. To the residue was added saturated Na₂CO₃ to adjust the pH>9. The aqueous layer was extracted with methylene chloride and the combined organic extracts was washed with water, brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column chromatography (methylene chloride to methylene chloride/ethyl acetate to ethyl acetate, 100% to 50% to 100%) to give 0.56 g (75%) of a solid: mp 141-142 °C [(mp 149 °C ; previously reported in J. Med. Chem. 36, 1194 (1993)].

20

Intermediate 3

5-Fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole. This compound was prepared from intermediate 2 in 88% yield following the reported procedure (Malleron et.al, J. Med..Chem. 1993, 36, 1194).

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Intermediate 4a,b

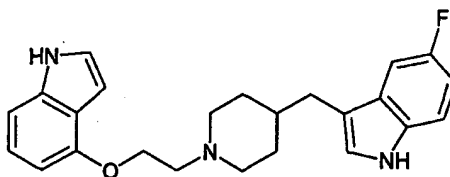
(4a) 2-(1*H*-Indol-4-yloxy)-chloroethane: This compound was prepared from 5-hydroxyindole and chloroethanol in 57 % using Mitsunobu conditions as reported in the literature (Mewshaw et al. J. Med. Chem. 1999, 42, 2007); mp 62-63 °C; ¹H NMR (CDCl₃) δ 3.88 (2H, t, J=6.2 Hz), 4.38 (2H, t, J=6.2 Hz), 6.52 (1H, d, J=7.3 Hz), 6.68 (1H, app. t, J=2.2 Hz), 7.02-7.12 (3H, m), 8.14 (1H, s).

30

- 5 (4b) 2-Methyl-2-(1H-indol-4-yloxy)-chloroethane was similarly prepared as described above as a yellow oil: (47 %); MS (EI) 209 (M+).

Example 1

10 **5-Fluoro-3-{1-[2-(1H-indol-4-yloxy)ethyl]-piperidin-4-ylmethyl}-1H-indole**

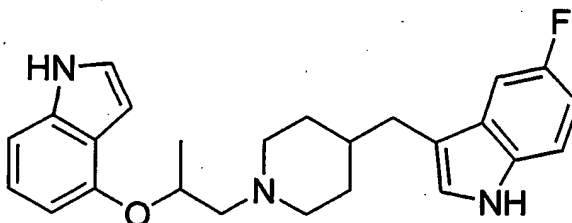


- To a solution of 5-fluoro-3-[(4-piperidinyl)methyl]-1H-indole (0.84 g, 3.6 mmol) in acetonitrile (50 mL) was added 4-(2-chloroethoxy)-1H-indole (0.59 g, 3.6 mmol), potassium carbonate (0.48 g) followed by addition of potassium iodide (0.60 g) at room temperature. The reaction mixture was heated to reflux for 5 h and cooled. The reaction mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography (methylene chloride/methanol, 95/5) to 0.45 g (38%) of a white foam. The free base (0.23 g, 0.59 mmol) was dissolved in ethyl acetate, and precipitated with one equivalent of HCl in ether to give the title compound (0.16 g, 62%) as monohydrochloride, 1.0 hydrate: mp 215 °C (dec.); ¹H NMR (DMSO, 400 MHz), δ 1.52-1.59 (m, 2H), 1.81-1.84 (m, 3H), 2.61 (d, 2H), 3.02-3.08 (m, 2H), 3.25-3.30 (m, 6H), 4.46 (t, 2H), 6.44-7.33 (m, 9H), 10.25 (br s, 1H), 10.98 (br s, 1H), 11.14 (br s, 1H); MS (FAB) m/z 392 (M+H)⁺.

5 Elemental Analysis Calcd for $C_{24}H_{26}FN_2O \cdot HCl \cdot H_2O$

Theory: C, 64.64; H, 6.55; N, 9.42.

Found: C, 64.76; H, 6.40.; N, 9.08.

Example 210 5-Fluoro-3-[[1-[2-(1H-indol-4-yloxy)propyl]-4-piperidiny]methyl]-1H-indole

To a solution of 5-fluoro-3-[(4-piperidinyl)methyl]-1H-indole (0.25 g, 1.1 mmol) in DMSO (15 mL) containing triethylamine (0.11 g, 1.3 mmol) was added 2-methyl-2-(1H-indol-4-yloxy)-chloroethane (0.3 g, 1.2 mmol). The reaction mixture was heated to 80 °C for 18 h and cooled. The reaction mixture was poured into water (100 mL), and extracted with methylene chloride. The organic layer was washed with water and dried over anhydrous sodium sulfate, filtered, and the solvent evaporated. Chromatography (6% methanol-methylene chloride containing 1 % ammonium hydroxide) afforded 72 mg (18 %) of a yellow foam. The hydrochloride salt was prepared by adding an excess 1 M HCl in ether to a solution of the free base in ethanol: mp 130-132 °C; MS (EI) m/z 406 (M⁺).

Elemental Analysis Calcd for $C_{25}H_{28}FN_3O \cdot HCl \cdot 1.5H_2O$

25 Theory: C, 64.02; H, 6.88; N, 8.96.

Found: C, 64.34; H, 6.52.; N, 8.65.

- 5 The results of the tests with compounds representative of this invention are given in the immediately following table.

Example No.	Ki (nM) Serotoinn Transporter [3H]paroxetine	Ki (nM) 5-HT1A [3H]DPAT
1	0.08	47
2	0.59	14 % @ 100 nM

- The compounds of this invention are useful in methods for the treatment of
- 10 depression as well as other serotonin-related disorders including, but not limited to, anxiety, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, sleep disorders, sexual dysfunction, bipolar disorders, psychosis, stress-related disorders, including post-traumatic stress disorders, Tourettes' syndrome, attention deficit disorder, with and without hyperactivity, alcohol and drug addiction,
- 15 Alzheimer's disease, Parkinson's disease, obesity and acute and chronic pain, including migraine pain. Chemical dependencies and addictions which may be treated with compounds of this invention include those to opiates, benzodiazepines, cocaine, nicotine and ethanol.

- 20 The compounds herein are also useful in methods of enhancing cognition in a mammal, preferably a human, particularly in a mammal experiencing a cognitive deficit as a result of or in association with Alzheimer's disease or Parkinson's disease.

5 Each of these methods of treatment comprise administering a pharmaceutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt thereof, to a mammal in need of such treatment or enhancement. A pharmaceutically or therapeutically effective amount of the compounds herein is understood to comprise an amount of the compound(s) in
10 question which will obtain at least a minimum of desired effect in preventing, treating, inhibiting or managing the symptoms or causes of the malady in question. More preferably, the amount will be the minimum needed to alleviate or remove the undesirable physiological consequences of the malady in question and inhibit or prevent their re-occurrence.

15 This invention also provides pharmaceutical formulations comprising a pharmaceutically or therapeutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

20 Applicable solid carriers for pharmaceutical compositions containing the compounds of this invention can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material.
25 In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate,
30 magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

 Liquid carriers may be used in preparing solutions, suspensions, emulsions,
35 syrups and elixirs. The active ingredient of this invention can be dissolved or

- 5 suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators.
- 10 Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an
- 15 oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

20 Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

25 Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

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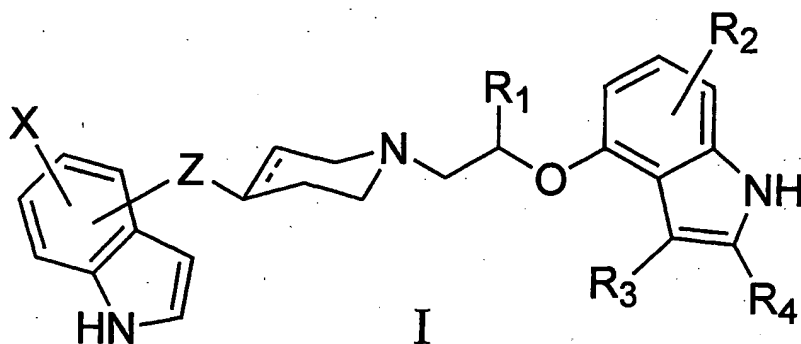
The dosage to be used in the treatment of a specific psychosis must be subjectively determined by the attending physician. The variables involved include the specific psychosis and the size, age and response pattern of the patient.

5 The therapeutically effective amount of the compounds of this invention that
is administered and the dosage regimen depends on a variety of factors, including the
weight, age, sex, and medical condition of the subject, the severity of the disease, the
route and frequency of administration, and the specific compound employed, and thus
may vary widely. However, it is believed that the pharmaceutical compositions may
10 contain the compounds of this invention in the range of about 0.1 to about 2000 mg,
preferably in the range of about 0.5 to about 500 mg and more preferably between
about 1 and about 100 mg. Projected daily dosages of active compound are about 0.01
to about 100 mg/kg body weight. The daily dose can be conveniently administered
two to four times per day.

15

CLAIMS:

1. A compound of the formula:



wherein:

R_1 is hydrogen or alkyl of from 1 to 6 carbon atoms;

R_2 , R_3 , and R_4 are each independently selected from hydrogen, alkyl of from 1 to 6 carbon atoms, or halogen;

X is selected from hydrogen, halogen, CN, or C_1 - C_6 alkoxy;

Z is $(CH_2)_n$ or carbonyl;

n is 1 or 2 ; and

the dashed line indicates an optional double bond;

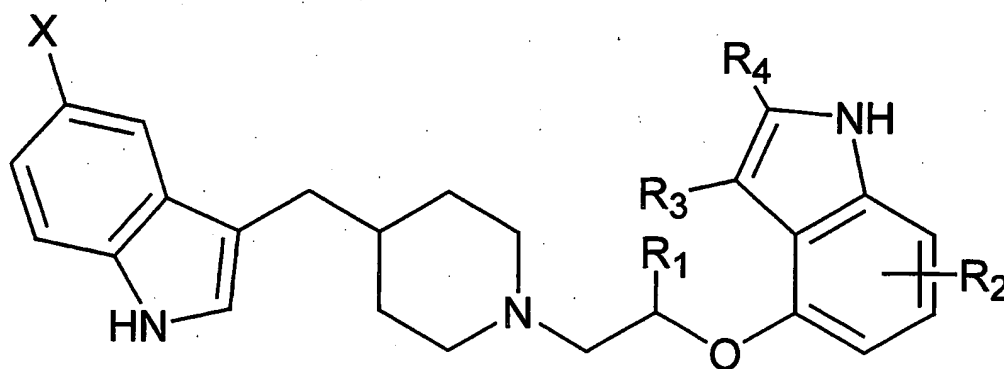
or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein R is hydrogen or alkyl .

3. A compound of Claim 1 or Claim 2 wherein R_2 , R_3 and R_4 independently represent hydrogen, alkyl of 1 to 3 carbon atoms, chlorine or fluorine.

4. A compound of any one of Claims 1 to 3 wherein X is hydrogen, fluorine, chlorine, CN or methoxy.
5. A compound of any one of Claims 1 to 4 wherein Z is $-\text{CH}_2-$
6. A compound of any one of Claims 1 to 5 wherein Z is bonded to the indole ring in the 3-position.

7. A compound of Claim 1 of the formula:



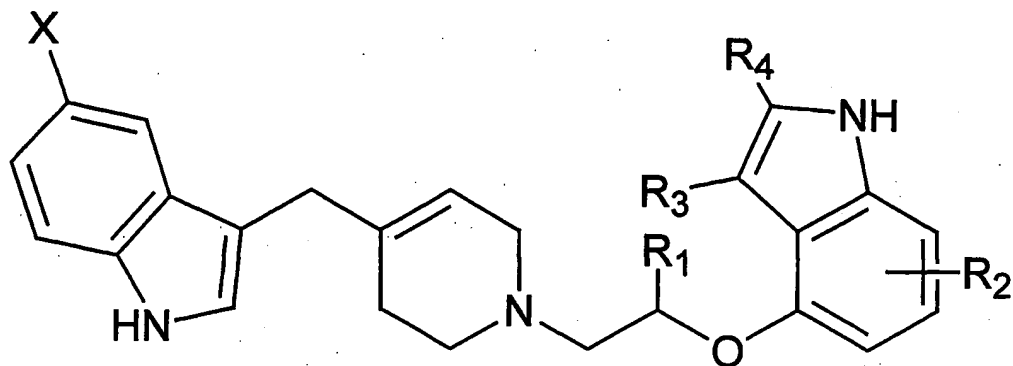
wherein:

X is selected from hydrogen, halogen, CN, or $\text{C}_1\text{--C}_6$ alkoxy;

R_1 is hydrogen or alkyl of from 1 to 3 carbon atoms; and

R_2 , R_3 , and R_4 are each independently selected from hydrogen, alkyl of from 1 to 6 carbon atoms, or halogen;
or a pharmaceutically acceptable salt thereof.

8. A compound of Claim 1 of the formula:



wherein:

X is selected from hydrogen, halogen, CN, or C₁-C₆ alkoxy;

R₁ is hydrogen or alkyl of from 1 to 3 carbon atoms; and

R₂, R₃, and R₄ are each independently selected from hydrogen, alkyl of from 1 to 6 carbon atoms, or halogen;
or a pharmaceutically acceptable salt thereof.

9. A compound of Claim 1 which is 5-Fluoro-3-{1-[2-(1*H*-indol-4-yloxy)ethyl]-piperidin-4-ylmethyl}-1*H*-indole, or a pharmaceutically acceptable salt thereof.

10. A compound of Claim 1 which is 5-Fluoro-3-[[1-[2-(1*H*-indol-4-yloxy)propyl]-4-piperidinyl]methyl]-1*H*-indole, or a pharmaceutically acceptable salt thereof.

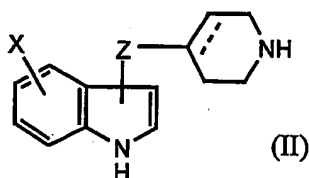
11. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of any one of Claims 1 to 10 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

12. A method of treating depression in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof.

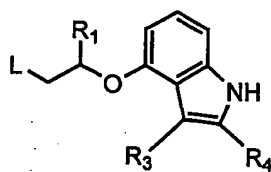
13. A method of treating anxiety in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof.

14. A process for preparing a compound of formula (I) as defined in claim 1 which comprises:

a) reacting a compound of formula



wherein X and Z are as defined above, with a compound of formula:



wherein R_1 , R_2 , R_3 and R_4 are as defined herein and is a leaving group,
or

b) converting a basic compound of formula I to an acid addition salt or vice versa.

or

c) isolating an isomer of a compound of formula I from a mixture of isomers.

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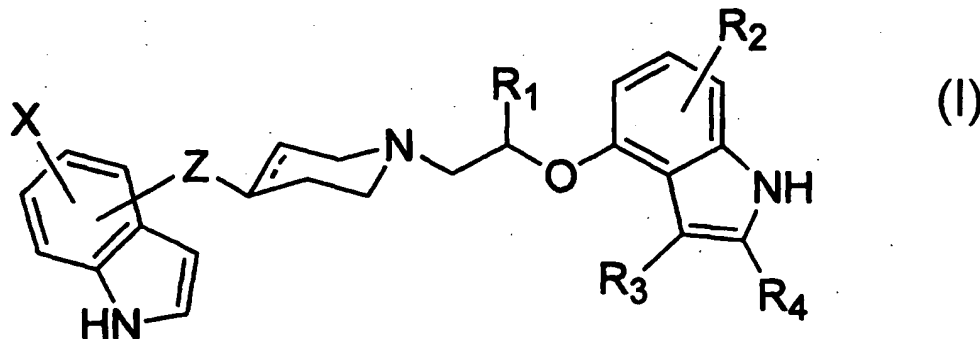
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(54) Title: ARYLOXY PIPERIDINYL INDOLES FOR TREATING DEPRESSION



(57) Abstract: This invention provides aryloxy indole derivatives which are useful for the treatment of diseases affected by disorders of the serotonin-affected neurological systems, such as depression and anxiety, the compounds having formula (I) wherein R₁ is H or alkyl; R₂, R₃, and R₄ are H, alkyl, or halogen; X is H, halogen, CN, or C₁-C₆ alkoxy; Z is (CH₂)_n or carbonyl; n is 1 or 2; and the dashed line indicates an optional double bond; or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/50019

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D209/08 A61K31/4045		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 722 941 A (LILLY CO ELI) 24 July 1996 (1996-07-24) claim 2; example 148 ---	1-14
Y	MALLERON, JEAN LUC ET AL: "New indole derivatives as potent and selective serotonin uptake inhibitors" J. MED. CHEM. (1993), 36(9), 1194-202 , XP000195950 cited in the application examples 3-10,13-21 ---	1-14
A	WO 96 26923 A (PF MEDICAMENT ;HALAZY SERGE (FR); PEREZ MICHEL (FR); JOHN GARETH () 6 September 1996 (1996-09-06) the whole document --- -/--	1-14
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *B* document member of the same patent family		
Date of the actual completion of the international search 29 May 2002		Date of mailing of the international search report 07/06/2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Grassl, D

INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/US 01/50019

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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